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News & views

Medical research

A next-wave inhalable dry powder COVID vaccine

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Current injectable COVID-19 vaccines are unable to induce robust immunity in the mucosal tissues lining the airways. A protein-based vaccine delivered to the lungs in the form of an inhaled dry powder shows promise as a way forward.

At present, COVID-19 vaccines are administered through injection into muscle. Although these shots are generally effective in providing protection against developing severe disease, they are less good at preventing infection by rapidly evolving variants of the coronavirus SARS-CoV-2. These vaccines are also less effective in high-risk populations, including older people and those with immunocompromised conditions, who require frequent booster injections. Intramuscularly injected vaccines cannot induce immunity in the mucosal tissues of the airways, which is the site of SARS-CoV-2 entry. Furthermore, current COVID-19 jabs require low-temperature 'cold-chain' conditions, from their manufacture to transportation and final storage and administration. Writing in *Nature*, Ye *et al.*[1] report a vaccine formulation that is not only able to induce respiratory mucosal immunity after local lung delivery, but is also inhaled as a dry powder – avoiding the need for cold chains and the use of needles.

The challenges that current COVID-19 vaccines face have led to calls for the development of next-generation vaccine strategies[2]. Such strategies are also important in preparing for future pandemics. One strategy being developed is to have shots deliverable through the airways, so as to generate mucosal immunity that today's injectable vaccines cannot provide[3,4].

Airway-delivered vaccines are commonly administered either as nasal sprays to the upper respiratory tract (URT) or by inhaled aerosols through the mouth to the lower respiratory tract (LRT), bypassing the URT (Fig. 1). Although aerosolized vaccines can be delivered nasally[5], they can spread to part of the brain (the olfactory bulb) in animals[6,7], thus posing a potential safety concern if used in humans. Except for a few COVID-19 vaccine candidates being developed for inhaled aerosol delivery, most of the ones under clinical development are based on a viral-vector system and are delivered through the nose[4]. All of these have a liquid formulation that requires a cold chain for transportation and storage.

To address this cold-chain requirement, Ye and colleagues made a vaccine that targets the coronavirus spike protein using peptide-based nanoparticles that are encapsulated into porous spheres measuring up to 4 micrometres in diameter. The authors used a freezing method to produce a dry-powder form of the vaccine that is stable at room temperature. They administered it by mouth to mice, hamsters and non-human primates, and the animals inhaled it into their lungs' terminal airways (small airway branches called bronchioles and gas-exchange sacs named alveoli). The microsphere structure used for the vaccine formulation prolongs the availability to the immune system of SARS-CoV-2 spike fragments termed antigens.

The study presents a unique approach for developing a next-generation COVID-19 vaccine strategy that directly targets the respiratory mucosal immune system and does not require a cold chain. Although the vaccine's safety and immune potency remain

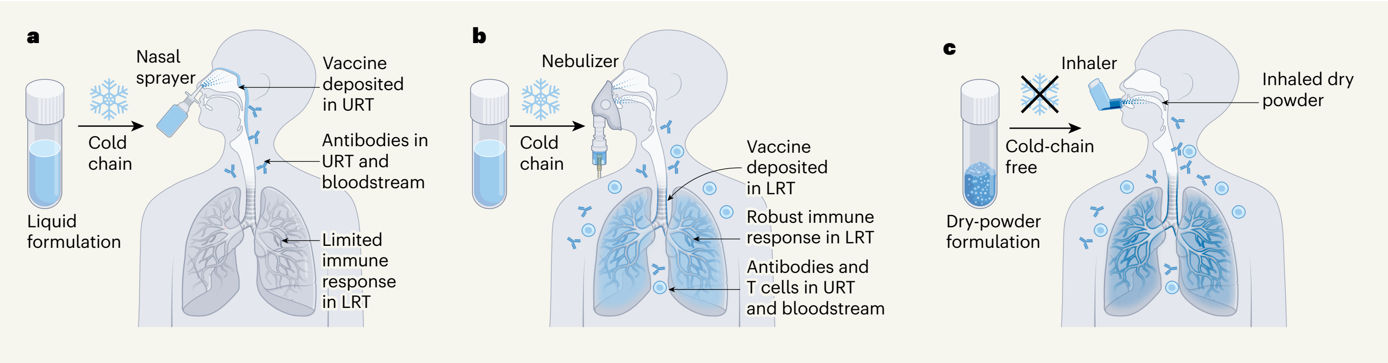

Figure 1 | Next-generation COVID vaccines. Current injected COVID-19 vaccines do not generate immunity in mucosal tissues that line the airways at the site of viral entry. Next-generation vaccines are being developed with the goal of boosting such immune responses. Liquid formulations require a cold chain of low-temperature conditions for vaccine transportation and storage, whereas dry-powder formulations can remain stable at room temperature. **a**, A liquid vaccine can be delivered to the human nose as droplets or mist by using a nasal sprayer. This results in a vaccine distribution and immunity (mediated by antibodies) that is limited mainly to the upper respiratory tract (URT) rather than the lower respiratory tract (LRT). **b**, Liquid vaccines can also be inhaled through the mouth using an aerosol-generating nebulizer. This deposits vaccine in the LRT, a site associated with effective induction of a variety of immune responses – antibodies; defences provided by immune cells called T cells; and 'trained' defences from the innate branch of the immune system (not shown) – while also maintaining immune responses in the URT and the bloodstream. **c**, Ye *et al.*[1] report their development of a dry powder vaccine that was tested in animal models. This is designed to be delivered orally as an aerosol, using an inhaler for LRT deposition.

to be tested by clinical trials in humans, if successful it would offer a streamlined way of administering a vaccine (without the need to reconstitute it in liquid) to induce respiratory mucosal immunity.

Ye and colleagues have shown that the dry-powder shot remains stable at room temperature for at least one month, but it will be essential to determine how long this stability lasts at room temperature and above, and how degradation of the vaccine affects immune potency. Furthermore, although the safety and potency of viral-vector vaccines inhaled as liquid aerosols (measuring 2–5 μm) have been well documented in humans[8,9], the question remains whether this 1–4-μm dry powder vaccine will be safe and drive an immune response when inhaled by people. Aerosol sizes determine vaccine-deposition sites in the LRT[10], so it is thought that targeting the terminal gas-exchange units in the lungs might cause undesired inflammation.

Besides safety considerations, intranasal and inhaled-aerosol vaccines differ in where they are distributed, and in where immunity is found in tissues[10]. Intranasal vaccine distribution and mucosal immunity is limited to the URT, whereas inhalation deposits vaccine in the LRT, resulting in mucosal immunity throughout the major airways in the lung. Thus, inhaled aerosol delivery through the mouth is a preferred method for the respiratory mucosal route of immunization. Although it is useful to undertake a multipronged approach to developing viral-vector and protein-based COVID-19 vaccines, including dry-powder formulations for inhalation, the safety and immune potency of these two platforms remain to be compared in humans.

It has been shown in animal models, and is clinically well documented, that viral-vector vaccines delivered to the LRT induce robust protective mucosal immunity that includes antibodies, immune cells called T cells, and 'trained' defences from the innate branch of the immune system (trained innate immunity)[4,8,11,12] (Fig. 1). It is unclear whether the type of vaccine developed by Ye and colleagues would induce trained innate immunity. Even so, protein-based formulations can be administered repeatedly when needed. By contrast, viral-vector jabs cannot be used repeatedly, because pre-existing immunity against the viral backbone of a viral-vector vaccine might weaken its potency after repeated immunization with the same type of shot.

Ye *et al.* packaged the receptor-binding portion of original (ancestral) SARS-CoV-2 spike antigen into the vaccine nanoparticles. After a single-dose inhalation, the vaccine was deposited to the LRT and induced antibodies and T cells that provided potent protection against SARS-CoV-2 infection in animal models. It also markedly blocked host-to-host viral transmission in hamster models.

To potentially broaden the vaccine's effectiveness against emerging variants of SARS-CoV-2, the authors demonstrated the feasibility of packaging the spike antigens of both ancestral and Omicron-variant viruses into the vaccine, but its protective efficacy was not assessed. However, frequently updating the spike antigen in vaccines might not be a viable solution to the emergence of new strains, because SARS-CoV-2 evolves rapidly and thereby evades targeting by antibodies[2,13]. In this regard, the key role of T-cell immunity for COVID-19 protection is increasingly recognized[14]. Thus, it will be crucial to include in next-generation vaccine designs not only the spike antigen but also antigens from internal regions of the virus known to be genetically more stable and evolutionarily conserved, so as to enhance the strength and breadth of the T-cell immunity generated[4,13].

One reason why fewer protein-based than viral-vector candidates have been clinically evaluated for respiratory mucosal delivery[4] is that immune stimulants (adjuvants) need to be included in the vaccine formulation[3]. Many adjuvants included in injectable vaccines are unsuitable for respiratory immunization. Ye and colleagues included a non-toxic bacterial protein called CTB as an adjuvant. CTB has been used safely in an orally administered human cholera vaccine[3], but it will be necessary to find out whether it is safe and effective when inhaled by humans. After intranasal delivery, CTB-adjuvanted vaccine is observed in the olfactory bulb in mice[6]. Some human participants in clinical trials developed a transient type of facial paralysis (Bell's palsy) after receiving intranasal vaccines containing a different type of bacterial toxin (LKT63) as an adjuvant[3].

It is time to develop next-generation vaccines that can be delivered to the respiratory tract, not only against SARS-CoV-2 but also against other infections. Moving promising candidates such as the one developed by Ye *et al.* from the bench into clinical trials will be a crucial step forwards. So far, few clinical COVID-19 vaccine trials have assessed the induction of mucosal immunity in the LRT after respiratory immunization. Future trials will need to fill this gap by using bronchoscopy to sample immune cells from the LRT and to search for biomarkers in the bloodstream that correlate with respiratory mucosal immunity. Furthermore, the delivery device, scalability and affordability of inhalable, protein-based nanoparticle vaccines also needs to be considered.

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